Rearrangement of 14 β -Hydroxy-12 β -sulfoxy-steroids to 13,17-Seco-12,17-cyclo-steroids; a 2D-NMR Analysis

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The rearrangement of 3-oxo-14 β -hydroxy-12 β -methanesulfoxy-card-20(22)-enolide and 14 β -hydroxy-12 β -methanesulfoxy-pregnane-3,20-dione during elimination of the sulfoxygroups was studied. By means of 2D-NMR analysis the structures were determined as 13,17-seco-12,17-cyclo-steroids.

Introduction

During our work on cardioactive steroids we studied the elimination of the 12 β -sulfoxy-group. It is well known that 12 β -tosyloxy- or 12 β -mesyloxy-steroids with C/D-*trans* juncture undergo elimination to yield C-nor-D-homo steroids with 12(13) or 13(18) double bonds [1–6]. The same rearrangement product was obtained by the reaction of a 12 β -tosyloxy-cardenolide [7] with C/D-*cis* juncture. No Grob-Fragmentation to 14-keto-12-en-13(14)-secosteroids was observed [7–10]. We now wish to report that the C-nor-D-homo-structure [7] proposed earlier for the rearrangement product must be corrected.

Results and Discussion

Elimination of the 12 β -hydroxy-group in digoxigenin (**1**) can be achieved under basic conditions if the 12 β -alcohol is converted to a sulfonic ester.

Originally it was proposed [7] that the elimination of the 12 β -tosyloxy-cardenolide (**4**) resulted in a C-nor-D-homo steroid (**6**).

The sulfoxy compounds could be synthesized in the following way. Digoxigenin (**1**) was oxidized to

digoxigenone (**2**) by either Pt/O₂ [11] or N-bromosuccinimide in acetone. The advantage of the latter reaction is the high selectivity for the 3 β -hydroxy group and a short reaction time. Also, with an excess of the bromo-compound no reaction at the 12 β -position took place, because bromination of acetone was preferred. Sulfonation of **2** with methanesulfonylchloride to **3** or toluene-4-sulfonylchloride to **4** [7] yielded the corresponding sulfonic esters. The mesylation to **3** in 30 min is much faster than the tosylation of **4** which takes 24 h. The sulfonic esters **3** and **4** were eliminated in pyridine or collidine yielding a rearranged product.

¹H NMR and ¹³C NMR agreed with three olefinic protons. A DEPT-experiment showed only one methyl- and four olefinic-carbon signals (Table I). Application of two dimensional Fourier-transform NMR-techniques [12] lead to the structure **5**.

The 2D-proton-proton shift correlation spectrum (Fig. 1) showed spin interaction between protons H(18)–H(12) and H(17)–H(22) which confirmed **5** as well as **6**. But, because a cross peak of

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Fig. 1. Homonuclear scalar correlated 2D- ^1H NMR spectrum and ^1H NMR spectrum (400 MHz in CDCl_3) of compound **5**.

Table I. ^{13}C chemical shifts for the cardenolids **2** (75 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$), **3** (75 MHz, CDCl_3), **5** (100 MHz, CDCl_3) and 13,17-seco-12,17-cyclo-pregnene **11** (100 MHz, CDCl_3) in ppm.

Position	2	3	5	11
1	37.13	36.88	38.07	38.23
2	36.86	36.56	37.35	37.45
3	214.11	211.50	212.80	212.94
4	42.23	41.95	42.56	42.68
5	43.99	43.44	43.65	43.85
6	26.73	27.42	27.59	27.76
7	21.40	21.20	16.69	19.81
8	41.12	41.11	49.64	50.57
9	33.77	33.62	39.15	39.22
10	35.28	35.24	35.08	35.16
11	29.95	28.15	21.00	21.44
12	74.45	85.07	50.00	49.65
13	56.23	54.66	145.63	145.17
14	85.40	85.68	79.79	80.19
15	32.99	33.10	31.24	23.46
16	27.54	27.40	25.12	31.79
17	45.92	45.60	44.07	57.62
18	9.17	10.23	112.09	113.07
19	22.47	22.38	21.43	21.34
20	176.35	174.35	171.28	208.70
21	74.33	73.58	72.63	27.90
22	117.31	118.24	116.36	—
23	176.01	173.14	173.78	—

H(18)–H(17) was not present, structure **6** could be excluded. The observation of a coupling between H(12)–H(17) proved the structure of the 13,17-seco-12,17-cyclo-cardenolide (**5**).

The rearrangement may be explained by the migration of C(17) to **5** whereas migration of C(14) could result in formation of **6**. Elimination of a proton from C(18) forms the exocyclic double bond.

To prove the general validity, the same rearrangement was also studied with a 20-keto side chain, instead of the butenolide system.

Starting with 3 β ,12 β -diacetoxy-14 β -hydroxy-androstane-17 β -carboxylic-acid (**7**) the 20-keto-pregnane (**8**) was obtained through methylation with methyl-lithium. Selective oxidation with *N*-bromosuccinimide as described before yielded the pregnane-3,20-dione (**9**). Reaction with methanesulfonylchloride in pyridine to **10** and elimination in collidine under reflux resulted in **11**.

^1H and ^{13}C NMR experiments indicated a rearrangement because of the presence of olefinic protons and only one methyl-signal. Structure **1** could be proven with 2D-proton-proton-shift-correlation (Fig. 2). Spin interaction between H(12)–H(18) and H(17)–H(12) agreed with the structure of the 13,17-seco-12,17-cyclo-steroid.

Fig. 2. Homonuclear-scalar correlated 2D- ^1H NMR spectrum (270 MHz) of compound **11**.

The 2D- ^1H ^{13}C shift correlation experiment allowed the determination of the chemical shift at H(16), H(12), H(11), H(9) and H(8) in the unresolved area of the 1D-proton spectrum (Fig. 3). The data confirmed the correlation from the cosy-experiment.

Intraperitoneal application of **5** in doses up to 50 mg/kg showed no toxicity in mice.

Further work to explain this rearrangement is presently under investigation.

Experimental

Melting points are uncorrected: Kofler hot stage apparatus. ^1H NMR and ^{13}C NMR spectra were taken on a Bruker AM-300 or AM-400. 2D-NMR experiments were carried out with a Varian XL-400 and a Jeol GX-270. IR-spectra were recorded on a Perkin Elmer 197 spectrometer. All the synthesized substances were analyzed for C,H and the results were within $\pm 0.3\%$ of theoretical values.

14 β -Hydroxy-3-oxo-13,17-seco-12,17-cyclo-card-13(18),20(22)-dienolide (**5**)

A solution of **3** (500 mg; 1.05 moles) in 6 ml pyridine was refluxed for 1 h. The solvent was evaporated *in vacuo* and the residue was dissolved in chloroform. After washing two times with 0.1 N HCl and drying over Na_2SO_4 the solvent was evaporated *in vacuo* to a white foam. The product was crystallized with ethyl-acetate/cyclohexane (330 mg; 85%); m.p. 195–197 °C. ^1H NMR (400 MHz) (CDCl_3): δ = 5.97 (1H; m; H-22); 5.15 (1H; pseudo s; H-18); 5.03 (1H; s; H-18); 4.74 and 4.68 (2H; d; d and d; d; J = 16 Hz; J = 1 Hz; J = 1.5 Hz; H-21 and H-21); 3.46 (1H; m; H-17); 0.99 (3H; s; H-19) ppm. MS (70 eV): 370 (10%); 352 (38%); 337 (8%); 335 (8%); 319 (6%); 282 (10%). IR (KBr) (cm^{-1}): 3100–3700 (OH, broad); 1780 and 1745 (lactone); 1705 (C=O); 1650 (C=C); 1620 (C=C); 890 ($\text{R}_2\text{C}=\text{CH}_2$): Reaction in collidine at 120 °C for 1 h yielded 93% **4** after usual workup.

Fig. 3. 2D- ^1H ^{13}C shift correlation contour plot of compound **11**.

3 β ,12 β ,14 β -Trihydroxy-5 β -pregnane-20-one (8)

Methyl-lithium (41 ml; 65.6 mmol) of a 1.6 M ether solution was added to 3 β ,14 β -diacetoxy-14 β -hydroxy-5 β -androstane-carboxylic acid (**7**) (3.7 g; 8.5 mmol) dissolved in 100 ml dry THF at 0 °C and stirred for 1 h. After hydrolysis with water and evaporation of THF under vacuum the residue was extracted three times with 50 ml chloroform. The organic extracts were washed with NaHCO₃ solution and dried over Na₂SO₄. Evaporation *in vacuo* yielded a syrup which could be crystallized with acetone/water (1.34 g; 45%); m.p. 204–206 °C. ¹H NMR (400 MHz) (CDCl₃): δ = 4.09 (1H; m; H-3); 3.55 (1H; m; H-12); 3.28 (1H; m; H-17); 2.27 (3H; s; H-21); 1.01 (3H; s; H-19); 0.89 (3H; s; H-18) ppm. MS (70 eV): 350 (1%); 332 (3%); 322 (3%); 317 (6%); 304 (6%); 265 (45%). IR (KBr) (cm⁻¹): 3200–3600 (OH, broad); 1695 (C=O).

12 β ,14 β -Dihydroxy-3-oxo-card-20(22)-enolide (2)

Digoxigenin (**1**) (2.3 g; 5.13 mmol) was dissolved in 160 ml acetone, 20 ml water and 3 ml acetic acid. After adding N-bromosuccinimide (1.5 g; 8.4 mmol) it was stirred for 1 h. Intermediately an orange colour appeared. The mixture was neutralized with NaHCO₃. Evaporation *in vacuo* and extraction of the water phase four times with 150 ml chloroform resulted, after evaporation, in a white foam. Crystals were obtained from acetone/water (1.8 g; 90%); m.p. 249–250 °C. ¹H NMR (300 MHz) (CDCl₃/CD₃OD): δ = 5.95 (1H; m; H-22); 4.98 and 4.84 (2H; d; d and d; d; J = 17 Hz; J = 1 Hz; J = 1.5 Hz; H-21 and H-21); 3.29–3.46 (2H; m; H-17 and H-12); 1.04 (3H; s; H-19); 0.85 (3H; s; H-18) ppm. MS (70 eV): 388 (10%); 370 (10%); 352 (5%); 337 (4%); 264 (54%); 260 (5%); 245 (8%); 235 (40%); 234 (32%). IR (KBr) (cm⁻¹): 2700–3200 (OH, broad); 1775 and 1740 (lactone); 1705 (C=O); 1630 (C=C).

14 β -Hydroxy-3-oxo-12 β -methanesulfoxy-card-20(22)-enolide (3)

The 3-keto-compound **2** (500 mg; 1.29 mmol) was dissolved in 20 ml pyridine and 0.33 ml methane-sulfonyl-chloride. After stirring for 30 min at room temperature the mixture was poured into water, acidified with HCl and extracted three times with 50 ml chloroform. Evaporation after drying over Na₂SO₄ yielded a white foam. The residue was crystallized with ethyl-acetate/cyclohexane. (520 mg; 90%); m.p. 121 °C. ¹H NMR (300 MHz) (CDCl₃):

δ = 5.92 (1H; m; H-22); 4.74–4.90 (2H; pseudo quartet; H-21 and H-21); 4.53 (1H; d; d; J = 3 Hz; J = 12 Hz; H-12); 3.26 (1H; d; d; J = 5 Hz; J = 9 Hz; H-17); 3.14 (3H; s; CH₃–SO₂–); 1.03 (3H; s; H-19); 0.89 (3H; s; H-18) ppm. MS (70 eV): 370 (1%); 352 (80%); 337 (22%); 334 (2%); 295 (30%); 280 (50%); 242 (80%); 229 (70%). IR (KBr) (cm⁻¹): 1780 and 1740 (lactone); 1705 (C=O); 1630 (C=C); 1330 (SO₂–O–).

12 β ,14 β -Dihydroxy-5 β -pregnane-3,20-dione (9)

20-Keto-pregnane **8** (1 g; 2.85 mmol) was oxidized in the same manner as described for **2**. Crystals were obtained from 2-propanol/water (872 mg; 88%); m.p. 176–177 °C. ¹H NMR (400 MHz) (CDCl₃): δ = 3.52 (1H; pseudo t; J = 6 Hz; J = 6.5 Hz; H-12); 3.33 (1H; d; d; J = 4 Hz; J = 12 Hz; H-17); 2.22 (3H; s; H-21); 1.02 (3H; s; H-18); 0.89 (3H; s; H-19) ppm. MS (70 eV): 348 (0.5%); 330 (8%); 320 (8%); 315 (10%); 263 (95%). IR (KBr) (cm⁻¹): 3200–3600 (OH, broad); 1705 (C=O); 1695 (C=O).

14 β -Hydroxy-13,17-seco-12,17-cyclo-5 β -pregn-13(18)-ene-3,20-dione (11)

The 3,20-diketo-pregnane (**9**) (800 mg; 2.3 mmol) was sulfonated as described for **3**.

Elimination was carried out in collidine like the reaction to **5**. The residue was crystallized with ethyl-acetate/hexane, m.p. 190–192 °C (635 mg; 84%). ¹H NMR (270 MHz) (CDCl₃): δ = 5.26 (1H; pseudo s; H-18); 5.05 (1H; pseudo s; H-18); 3.35 (1H; m; H-17); 2.13 (3H; s; H-21); 0.93 (3H; s; H-19) ppm. MS (70 eV): 330 (6%); 312 (8%); 207 (10%); 269 (58%). IR (KBr) (cm⁻¹): 3200–3600 (OH-broad); 1705 (C=O); 1695 (C=O); 1640 (C=C); 890 (R₂C=CH₂).

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